CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074762

Trade Name : GUANFACINE TABLETS USP

Generic Name: Guanfacine Tablets USP 1mg(base) and 2mg(base)

Sponsor : Royce Laboratories, Inc.

Approval Date: June 25, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074762

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Microbiology Review(s)				
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Bioequivalence Review(s)	X			
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Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074762

APPROVAL LETTER

ANDA 74-762

Royce Laboratories, Inc.
Attention: William Stahovec
16600 NW 54th Avenue
Miami, FL 33014

Dear Sir:

Reference is made to your abbreviated new drug application dated October 3, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Guanfacine Tablets USP, 1 mg (base) and 2 mg (base).

Reference is also made to your amendments dated November 21, 1995; January 25, July 15, July 23 and October 15, 1996; and May 29 and June 4, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Guanfacine Hydrochloride Tablets USP, 1 mg (base) and 2 mg (base) to be bioequivalent and therefore, therapeutically equivalent to those of the listed drug (Tenex® Tablets, 1 mg (base) and 2 mg (base), respectively, of A.H. Robins Company). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

[redacted]

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign, at the time of their initial use, be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253.

Sincerely yours,

[redacted] 6/24/97

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074762

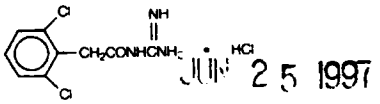
FINAL PRINTED LABELING

GUANFACINE TABLETS, USP

DESCRIPTION

Guanfacine hydrochloride is a centrally acting antihypertensive with α_2-adrenoceptor agonist properties in tablet form for oral administration.

The chemical name of guanfacine hydrochloride is *N*-amidino-2-(2,6-dichlorophenyl) acetamide hydrochloride and its molecular weight is 282.56. Its structural formula is:



$C_9H_9Cl_2N_3O \cdot HCl$

Guanfacine hydrochloride is a white to off-white powder; sparingly soluble in water and alcohol and slightly soluble in acetone.

Each tablet for oral administration contains guanfacine hydrochloride equivalent to 1 mg or 2 mg of guanfacine. In addition, each tablet contains the following inactive ingredients: crospovidone, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, and stearic acid. The 1 mg tablets also contain FD&C Red #40 aluminum lake; the 2 mg tablets contain D&C Yellow #10 aluminum lake.

CLINICAL PHARMACOLOGY

Guanfacine hydrochloride is an orally active antihypertensive agent whose principal mechanism of action appears to be stimulation of central α_2-adrenergic receptors. By stimulating these receptors, guanfacine reduces sympathetic nerve impulses from the vasomotor center to the heart and blood vessels. This results in a decrease in peripheral vascular resistance and a reduction in heart rate.

The dose-response relationship for blood pressure and adverse effects of guanfacine given once a day as monotherapy has been evaluated in patients with mild to moderate hypertension. In this study patients were randomized to placebo or to 0.5 mg, 1 mg, 2 mg, 3 mg, or 5 mg of guanfacine hydrochloride. Results are shown in the following table. A useful effect was not observed overall until doses of 2 mg were reached, although responses in white patients were seen at 1 mg; 24 hour effectiveness of 1 mg to 3 mg doses was documented using 24 hour ambulatory monitoring. While the 5 mg dose added an increment of effectiveness, it caused an unacceptable increase in adverse reactions.

Mean Changes (mm Hg) from Baseline in Seated Systolic and Diastolic Blood Pressure for Patients Completing 4 to 6 Weeks of Treatment with Guanfacine Monotherapy

Mean Change S/D* Seated	n= (range)	Placebo	0.5 mg	1 mg	2 mg	3 mg	5 mg
White Patients	11-30	-1/-5	-6/-8	-8/-9	-12/-11	-15/-12	-18/-16
Black patients	8-28	-3/-5	0/-2	-3/-5	-7/-7	-8/-9	-19/-15

*S/D= Systolic/diastolic blood pressure.

Controlled clinical trials in patients with mild to moderate hypertension who were receiving a thiazide-type diuretic have defined the dose-response relationship for blood pressure response and adverse reactions of guanfacine given at bedtime and have shown that the blood pressure response to guanfacine can persist for 24 hours after a single dose. In the 12-week placebo-controlled dose-response study, patients were randomized to placebo or to doses of 0.5, 1, 2, and 3 mg of guanfacine, in addition to 25 mg chlorthalidone, each given at bedtime. The observed mean changes from baseline, tabulated below, indicate the similarity of response for placebo and the 0.5 mg dose. Doses of 1, 2, and 3 mg resulted in decreased blood pressure in the sitting position with no real differences among the three doses. In the standing position, there was some increase in response with dose.

Mean Decreases (mm Hg) in Seated and Standing Blood Pressure for Patients Treated with Guanfacine in Combination with Chlorthalidone

Mean Change n=	Placebo 63	0.5 mg 63	1 mg 64	2 mg 58	3 mg 59
S/D* Seated	-5/-7	-5/-6	-14/-13	-12/-13	-16/-13
S/D* Standing	-3/-5	-5/-4	-11/-9	-9/-10	-15/-12

*S/D= Systolic/diastolic blood pressure

While most of the effectiveness of guanfacine in combination (and as a monotherapy in white patients) was present at 1 mg, adverse reactions at this dose were not clearly distinguishable from those associated with placebo. Adverse reactions were clearly present at 2 and 3 mg (see **Adverse Reactions**)

In a second 12-week placebo-controlled study of 1, 2 or 3 mg of guanfacine hydrochloride administered with 25 mg chlorthalidone once daily, a significant decrease in blood pressure was maintained for a full 24 hours after dosing. While there was no significant difference between the 12 and 24 hour blood pressure readings, the fall in blood pressure at 24 hours was numerically smaller, suggesting possible escape of blood pressure in some patients and the need for individualization of therapy.

In a double-blind, randomized trial, either guanfacine or clonidine was given at recommended doses with 25 mg chlorthalidone for 24 weeks, and then abruptly discontinued. Results showed equal degrees of blood pressure reduction with the two drugs, and there was no tendency for blood pressures to increase despite maintenance of the same daily dose of the two drugs. Signs and symptoms of rebound phenomena were infrequent upon discontinuation of either drug. Abrupt withdrawal of clonidine produced a rapid return of diastolic and especially, systolic blood pressure to approximately pre-treatment levels, with occasional values significantly greater than baseline, whereas guanfacine withdrawal produced a more gradual increase to pre-treatment levels, but also with occasional values significantly greater than baseline.

Pharmacodynamics: Hemodynamic studies in man showed that the decrease in blood pressure observed after a single-dose or long-term oral treatment with guanfacine was accompanied by a significant decrease in peripheral resistance and a slight reduction in heart rate (5 beats/min). Cardiac output under conditions of rest or exercise was not altered by guanfacine.

Guanfacine lowered elevated plasma renin activity and plasma catecholamine levels in hypertensive patients, but this does not correlate with individual blood-pressure responses.

Growth hormone secretion was stimulated with single oral doses of 2 and 4 mg of guanfacine. Long-term use of guanfacine had no effect on growth hormone levels.

Guanfacine had no effect on plasma aldosterone. A slight but insignificant decrease in plasma volume occurred after one month of guanfacine therapy. There were no changes in mean body weight or electrolytes.

Pharmacokinetics: Relative to an intravenous dose of 3 mg, the absolute oral bioavailability of guanfacine is about 80%. Peak plasma concentrations occur from 1 to 4 hours with an average of 2.6 hours after single oral doses or at steady state.

The area under the concentration-time curve (AUC) increases linearly with the dose.

In individuals with normal renal function, the average elimination half-life is approximately 17 hr (range 10-30 hr). Younger patients tend to have shorter elimination half-lives (13-14 hr) while older patients tend to have half-lives at the upper end of the range. Steady state blood levels were attained within 4 days in most subjects.

In individuals with normal renal function, guanfacine and its metabolites are excreted primarily in the urine. Approximately 50% (40-75%) of the dose is eliminated in the urine as unchanged drug; the remainder is eliminated mostly as conjugates of metabolites produced by oxidative metabolism of the aromatic ring.

The guanfacine-to-creatinine clearance ratio is greater than 1, which would suggest that tubular secretion of drug occurs.

The drug is approximately 70% bound to plasma proteins, independent of drug concentration.

The whole body volume of distribution is high (a mean of 8.3 L/kg), which suggests a high distribution of drug to the tissues.

The clearance of guanfacine in patients with varying degrees of renal insufficiency is reduced, but plasma levels of drug are only slightly increased compared to patients with normal renal function. When prescribing for patients with renal impairment, the low end of the dosing range should be used. Patients on dialysis also can be given usual doses of guanfacine hydrochloride as the drug is poorly dialyzed.

INDICATIONS AND USAGE

Guanfacine tablets are indicated in the management of hypertension. Guanfacine may be given alone or in combination with other antihypertensive agents, especially thiazide-type diuretics.

CONTRAINDICATIONS

Guanfacine hydrochloride is contraindicated in patients with known hypersensitivity to guanfacine hydrochloride.

PRECAUTIONS

General: Like other hypertensive agents, guanfacine should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease, or chronic renal or hepatic failure.

Sedation: Guanfacine like other orally active central α-2 adrenergic agonists, causes sedation or drowsiness, especially when beginning therapy. These symptoms are dose-related (see **ADVERSE REACTIONS**). When guanfacine is used with other centrally active depressants (such as phenothiazines, barbiturates, or benzodiazepines), the potential for additive sedative effects should be considered.

Rebound: Abrupt cessation of therapy with orally active central α-2 adrenergic agonists may be associated with increases (from depressed on-therapy levels) in plasma and urinary catecholamines, symptoms of "nervousness and anxiety" and, less commonly, increases in blood pressure to levels significantly greater than those prior to therapy.

Information for Patients: Patients who receive guanfacine should be advised to exercise caution when operating dangerous machinery or driving motor vehicles until it is determined that they do not become drowsy or dizzy from the medication. Patients should be warned that their tolerance for alcohol and other CNS depressants may be diminished. Patients should be advised not to discontinue therapy abruptly.

Laboratory Tests: In clinical trials, no clinically relevant laboratory test abnormalities were identified as causally related to drug during short-term treatment with guanfacine.

Drug Interactions: The potential for increased sedation when guanfacine is given with other CNS-depressant drugs should be appreciated.

The administration of guanfacine concomitantly with a known microsomal enzyme inducer (phenobarbital or phenytoin) to two patients with renal impairment reportedly resulted in significant reductions in elimination half-life and plasma concentration. In such cases, therefore, more frequent dosing may be required to achieve or maintain the desired hypotensive response. Further, if guanfacine is to be discontinued in such patients, careful tapering of the dosage may be necessary in order to avoid rebound phenomena (see ***Rebound*** above).

Anticoagulants: Ten patients who were stabilized on oral anticoagulants were given guanfacine, 1 to 2 mg/day, for 4 weeks. No changes were observed in the degree of anticoagulation.

In several well-controlled studies, guanfacine was administered together with diuretics with no drug interactions reported. In the long-term safety studies, guanfacine was given concomitantly with many drugs without evidence of any interactions. The principal drugs given (number of patients in parentheses) were: cardiac glycosides (115), sedatives and hypnotics (103), coronary vasodilators (52), oral hypoglycemics (45), cough and cold preparations (45), NSAIDs (38), antihyperlipidemics (29), antigout drugs (24), oral contraceptives (18), bronchodilators (13), insulin (10), and beta blockers (10).

Drug/Laboratory Test Interactions: No laboratory test abnormalities related to the use of guanfacine have been identified.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No carcinogenic effect was observed in studies of 78 weeks in mice at doses more than 150 times the maximum recommended human dose and 102 weeks in rats at doses more than 100 times the maximum recommended human dose. In a variety of test models, guanfacine was not mutagenic.

No adverse effects were observed in fertility studies in male and female rats.

Pregnancy Category B: Administration of guanfacine to rats at 70 times the maximum recommended human dose and to rabbits at 20 times the maximum recommended human dose resulted in no evidence of harm to the fetus. Higher doses (100 and 200 times the maximum recommended human dose in rabbits and rats respectively) were associated with reduced fetal survival and maternal toxicity. Rat experiments have shown that guanfacine crosses the placenta.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: Guanfacine is not recommended in the treatment of acute hypertension associated with toxemia of pregnancy. There is no information available on the effects of guanfacine on the course of labor and delivery.

Nursing Mothers: It is not known whether guanfacine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when guanfacine hydrochloride is administered to a nursing woman. Experiments with rats have shown that guanfacine is excreted in the milk.

Pediatric Use: Safety and effectiveness in pediatric patients under 12 years of age have not been demonstrated. Therefore, the use of guanfacine hydrochloride in this age group is not recommended.

ADVERSE REACTIONS

Adverse reactions noted with guanfacine are similar to those of other drugs of the central α-2 adrenoreceptor agonist class: dry mouth, sedation (somnolence), weakness (asthenia), dizziness, constipation, and impotence. While the reactions are common, most are mild and tend to disappear on continued dosing.

Skin rash with exfoliation has been reported in a few cases; although clear cause and effect relationships to guanfacine could not be established, should a rash occur, guanfacine should be discontinued and the patient monitored appropriately.

In the dose-response monotherapy study described under **CLINICAL PHARMACOLOGY**, the frequency of the most commonly observed adverse reactions showed a dose relationship from

Adverse Reaction	Placebo n=80
Dry Mouth	0%
Somnolence	8%
Asthenia	0%
Dizziness	8%
Headache	8%
Impotence	0%
Constipation	0%
Fatigue	2%

The percent of patients who dropped out because o

	Placebo
Percent dropouts	0%

The most common reasons for dropouts among pat
ness, and constipation.

In the 12-week, placebo-controlled, dose-response s
of the most commonly observed adverse reactions

Adverse Reaction	Placebo n=79
Dry Mouth	5 (7%)
Somnolence	1 (1%)
Asthenia	0 (0%)
Dizziness	2 (2%)
Headache	3 (4%)
Impotence	1 (1%)
Constipation	0 (0%)
Fatigue	3 (3%)

There were 41 premature terminations because of a
at which the dropout occurred were as follows:

Dose:	Placebo
Percent dropouts	6.9%

Reasons for dropouts among patients who receiv
tence, insomnia, constipation, syncope, urinary in
in a second 12-week placebo-controlled combinati
1-mg increments at 3-week intervals, i.e., a setting
dry mouth, 47%; constipation, 16%; fatigue, 12%.
Reasons for dropouts among patients who receive
fusion, depression, and palpitations.
In the clonidine/guanfacine comparison described
follows

Adverse Reaction	Guanfacine (n=279)	Clonidine (n=279)
Dry Mouth	30%	37%
Somnolence	21%	35%
Dizziness	11%	6%
Constipation	10%	5%
Weakness	9%	8%
Headache	4%	4%
Insomnia	4%	3%

Adverse reactions occurring in 3% or less of patients in the three controlled trials of guanfacine with a diuretic were

Cardiovascular-	bradycardia, palpitations, substernal pain
Gastrointestinal-	abdominal pain, diarrhea, dyspepsia, dysphagia, nausea
CNS-	amnesia, confusion, depression, insomnia, libido decrease
ENT disorders-	rhinitis, taste perversion, tinnitus
Eye disorders-	conjunctivitis, iritis, vision disturbance
Musculoskeletal-	leg cramps, hypokinesia
Respiratory-	dyspnea
Dermatologic-	dermatitis, pruritus, purpura, sweating
Urogenital-	testicular disorder, urinary incontinence
Other-	malaise, paresthesia, paresis

Adverse reaction reports tend to decrease over time. In an open-label trial of one year's duration, 580 hypertensive subjects were given guanfacine, titrated to achieve goal blood pressure, alone (51%) with diuretic (38%), with beta blocker (3%), with diuretic plus beta blocker (6%), or with diuretic plus vasodilator (2%). The mean daily dose of guanfacine reached was 0.7 mg.

Adverse Reaction	Incidence of adverse reactions at any time during the study n= 580	Incidence of adverse reactions at end of one year n=580
Dry Mouth	60%	15%
Drowsiness	33%	6%
Dizziness	15%	1%
Constipation	14%	3%
Weakness	5%	1%
Headache	4%	0.2%
Insomnia	5%	0%

There were 52 (8.9%) dropouts due to adverse effects in this 1-year trial. The causes were: dry mouth (n=20), weakness (n=12), constipation (n=7), somnolence (n=3), nausea (n=3), orthostatic hypotension (n=2), insomnia (n=1), rash (n=1), nightmares (n=1), headache (n=1), and depression (n=1).

Postmarketing Experience: An open-label postmarketing study involving 21,718 patients was conducted to assess the safety of guanfacine (as the hydrochloride) 1 mg/day given at bedtime for 28 days. Guanfacine was administered with or without other antihypertensive agents. Adverse events reported in the postmarketing study at an incidence greater than 1% included dry mouth, dizziness, somnolence, fatigue, headache and nausea. The most commonly reported adverse events in this study were the same as those observed in controlled clinical trials.

Less frequent, possibly guanfacine-related events observed in the post-marketing study and/or reported spontaneously include:

BODY AS A WHOLE	asthenia, chest pain, edema, malaise, tremor
CARDIOVASCULAR	bradycardia, palpitations, syncope, tachycardia
CENTRAL NERVOUS SYSTEM	paresthesias, vertigo
EYE DISORDERS	blurred vision
GASTROINTESTINAL SYSTEM	abdominal pain, constipation, diarrhea, dyspepsia
LIVER AND BILIARY SYSTEM	abnormal liver function tests
MUSCULO-SKELETAL SYSTEM	arthralgia, leg cramps, leg pain, myalgia
PSYCHIATRIC	agitation, anxiety, confusion, depression, insomnia, nervousness
REPRODUCTIVE SYSTEM, MALE	impotence
RESPIRATORY SYSTEM	dyspnea
SKIN AND APPENDAGES	alopecia, dermatitis, exfoliative dermatitis, pruritus, rash
SPECIAL SENSES	alterations in taste
URINARY SYSTEM	nocturia, urinary frequency

Rare, serious disorders with no definitive cause and affect relationship to guanfacine have been reported spontaneously and/or in the post-marketing study. These events include acute renal failure, cardiac fibrillation, cerebrovascular accident, congestive heart failure, heart block, and myocardial infarction.

DRUG ABUSE AND DEPENDENCE

No reported abuse or dependence has been associated with the administration of guanfacine.

OVERDOSAGE

Signs and Symptoms. Drowsiness, lethargy, bradycardia and hypotension have been observed following overdose with guanfacine.

A 25-year-old female intentionally ingested 60 mg. She presented with severe drowsiness and bradycardia of 45 beats/minute. Gastric lavage was performed and an infusion of isoproterenol (0.8 mg in 12 hours) was administered. She recovered quickly and without sequelae.

A 28-year-old female who ingested 30 to 40 mg developed only lethargy, was treated with activated charcoal and a cathartic, was monitored for 24 hours, and was discharged in good health.

A 2-year-old male weighing 12 kg, who ingested up to 4 mg of guanfacine, developed lethargy. Gastric lavage (followed by activated charcoal and sorbitol slurry via NG tube) removed some tablet fragments within 2 hours after ingestion, and vital signs were normal. During 24-hour observation in ICU, systolic pressure was 58 and heart rate 70 at 16 hours post-ingestion. No intervention was required, and child was discharged fully recovered the next day.

Treatment of Overdosage: Gastric lavage and supportive therapy as appropriate. Guanfacine is not dialyzable in clinically significant amounts (2.4%).

DOSAGE AND ADMINISTRATION

The recommended initial dose of guanfacine (as the hydrochloride) when given alone or in combination with another hypertensive drug is 1 mg daily given at bedtime to minimize somnolence. If after 3 to 4 weeks of therapy, 1 mg does not give a satisfactory result, a dose of 2 mg may be given, although most of the affect of guanfacine is seen at 1 mg (see Clinical Pharmacology). Higher daily doses have been used, but adverse reactions increase significantly with doses above 3 mg/day.

The frequency of rebound hypertension is low, but it can occur. When rebound occurs, it does so after 2 to 4 days, which is delayed compared with clonidine hydrochloride. This is consistant with the longer half-life of guanfacine. In most cases, after abrupt withdrawal of guanfacine, blood pressure returns to pretreatment levels slowly (within 2-4 days) without ill effects.

HOW SUPPLIED

Guanfacine Tablets, USP, 1 mg contain guanfacine hydrochloride equivalent to 1 mg of guanfacine, and are pink, biconvex, rounded square, unscored, compressed tablets. They are debossed 407 over 1 on one side and the Royce logo on the other side.

SIZE	ROYCE NDC NUMBER
Bottles of 100	51875-0407-1
Bottles of 500	51875-0407-2
Bottles of 1000	51875-0407-4

Guanfacine Tablets, 2 mg contain guanfacine hydrochloride equivalent to 2 mg of guanfacine, and are yellow, biconvex rounded square, unscored, compressed tablets. They are debossed 408 over 2 on one side and the Royce logo on the other side.

SIZE	ROYCE NDC NUMBER
Bottles of 100	51875-0408-1
Bottles of 500	51875-0408-2
Bottles of 1000	51875-0408-4

Store at controlled room temperature 15°-30° C (59°-86° F).
Dispense in a tight, light-resistant container as defined in the USP
Caution - Federal law prohibits dispensing without prescription

Royce Laboratories, Inc.
16600 NW 54 Avenue, Miami, Florida 33014

Revised 5/96

Each Tablet Contains:
Guanfacine Hydrochloride, USP
equivalent to ..... 2 mg guanfacine
USUAL DOSAGE:
See accompanying product literature.
Store at controlled room temperature
15°-30°C (59°-86°F).
Dispense in a tight, light-resistant
container as defined in the USP.

Royce™ NDC 51875-0408-4

GUANFACINE TABLETS, USP

2 mg

CAUTION: Federal law prohibits dispensing without prescription.

1000 Tablets

Mfd. by: Royce Laboratories, Inc., Miami, FL 33014

N 25 1

Batch No.:

Exp. Date:

N 51875-0408-4 5

Each Tablet Contains:
Guanfacine Hydrochloride, USP
equivalent to ..... 2 mg guanfacine

USUAL DOSAGE:
See accompanying product literature.
Store at controlled room temperature
15°-30°C (59°-86°F).
Dispense in a tight, light-resistant
container as defined in the USP.

Royce™ NDC 51875-0408-2

GUANFACINE TABLETS, USP

2 mg

CAUTION: Federal law prohibits dispensing without prescription.

500 Tablets

Mfd. by: Royce Laboratories, Inc., Miami, FL 33014

25 1997

Batch No.:

Exp. Date:

N 51875-0408-2 1

Each Tablet Contains:
Guanfacine Hydrochloride, USP
equivalent to ..... 2 mg guanfacine
USUAL DOSAGE:
See accompanying product literature.
Store at controlled room temperature
15°-30°C (59°-86°F).
Dispense in a tight, light-resistant
container as defined in the USP.

Royce™ NDC 51875-0408-1

GUANFACINE TABLETS, USP

2 mg

CAUTION: Federal law prohibits dispensing without prescription.

100 Tablets

Mfd. by: Royce Laboratories, Inc., Miami, FL 33014

Batch No.:
Exp. Date:

3 51875-0408-1 4

Each Tablet Contains:
Guanfacine Hydrochloride, USP
equivalent to ..... 1 mg guanfacine
USUAL DOSAGE:
See accompanying product literature.
Store at controlled room temperature
15°-30°C (59°-86°F).
Dispense in a tight, light-resistant
container as defined in the USP.

Royce™ NDC 51875-0407-4

GUANFACINE TABLETS, USP

CAUTION: Federal law prohibits dispensing without prescription.

1000 Tablets

Mfd. by: Royce Laboratories, Inc., Miami, FL 33014

: 5 1997

Batch No.:

Exp. Date:

N 3 51875-0407-4 6

Each Tablet Contains:
Guanfacine Hydrochloride, USP
equivalent to ..... 1 mg guanfacine

USUAL DOSAGE:
See accompanying product literature.
Store at controlled room temperature
15°-30°C (59°-86°F).
Dispense in a tight, light-resistant
container as defined in the USP.

Royce TM NDC 51875-0407-2

GUANFACINE TABLETS, USP

CAUTION: Federal law prohibits dispensing without prescription.

500 Tablets

Mfd. by: Royce Laboratories, Inc., Miami, FL 33014

2 5 199

Batch No.:

Exp. Date:

N 3 51875-0407-2 2

MARGO

Each Tablet Contains:
Guanfacine Hydrochloride, USP
equivalent to ..... 1 mg guanfacine
USUAL DOSAGE:
See accompanying product literature.
Store at controlled room temperature
15°-30°C (59°-86°F).
Dispense in a tight, light-resistant
container as defined in the USP.

Royce™ NDC 51875-0407-1

GUANFACINE TABLETS, USP

CAUTION: Federal law prohibits dispensing without prescription.

100 Tablets

Mfd. by: Royce Laboratories, Inc., Miami, FL 33014

5 199

Batch No.:
Exp. Date:

3 51875-0407-1 5

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074762

CHEMISTRY REVIEW(S)

1. CHEMIST'S REVIEW NO.2

2. ANDA # 74-762

3. NAME AND ADDRESS OF APPLICANT

Royce Laboratories, Inc
16600 N.W. 54 Avenue
Miami, FL 33014

4. LEGAL BASIS OF SUBMISSION:

No Patent or any marketing exclusivity rights are in effect.

7. NONPROPRIETARY NAME

Guanfacine Hydrochloride

9. AMENDMENTS AND OTHER DATES:

Original 10/3/95
Amendment 11/21/95
Amendment 7/15/96
Amendment 10/15/96
Amendment 5/29/97
Amendment 6/4/97

10. PHARMACOLOGICAL CATEGORY

Antihypertensive

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

[redacted]

13. DOSAGE FORM

Tablets

1 mg and 2 mg

15. CHEMICAL NAME AND STRUCTURE

N-amidino-2-(2,6-dichlorophenyl) acetamide hydrochloride.

16. COMMENTS

17. CONCLUSIONS AND RECOMMENDATIONS

The application is approvable

19. REVIEWER: [redacted] DATE COMPLETED: 6/12/97

Nashed E. Nashed, Ph.D. 6/9/97 6/19/97

Supervisor: Paul Schwartz, Ph.D. [redacted]

cc: ANDA 74-762.3
Division File
Field Copy

Endorsements: [redacted] 6/9/97

HFD-627/N.Nashed, Ph.D./ 6/13/97
HFD-627/P.Schwartz, Ph.D./
X:\NEW\FIRMSNZ\ROYCE\LTRS&REV\74-762.3
F/T by: bc/6-12-97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074762

BIOEQUIVALENCE REVIEW(S)

ANDA 74-762

NOV 12 1996

Royce Laboratories, Inc.
Attention: Loren Gelber, Ph.D.
16600 NW 54 Ave
Miami FL 33014

Dear Madam:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Guanfacine Hydrochloride Tablets 1 mg and 2 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The following dissolution testing will need to be incorporated into your stability and quality control programs:

   The dissolution testing should be conducted in 500 mL of water at 37°C using USP 23 apparatus II (paddle) at 50 rpm. The test product should meet the following specification:

   Not less than [redacted] Q) of the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

[redacted]

Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

NOV 6 1996

Guanfacine HCl Tablets	Royce Laboratories, Inc.
1 mg and 2 mg	Miami, FL
ANDA #74-762	Submission Date:
Reviewer: Moheb H. Makary	July 15, 1996
WP 74762SDW.796	July 23, 1996

Review of An Amendment to a Bioequivalence Study

I. Objective:

The firm has replied to the reviewer's comments made in the review of the October 3, 1995 submission (bioequivalence study on Guanfacine HCl Tablets, 2 mg, dissolution data and waiver request, reviewed by Dr. James D. Henderson).

II. Comment #1

The firm was advised to submit data to support the long-term stability of Guanfacine in frozen study samples for the period equal to the time from the first sample was collected to the day [redacted]

Reply to the Comment

The firm's response to the comment is acceptable.

Comment #2

The firm was advised to provide a table of sample identification for all 32 samples listed as "lost in processing". In addition, the firm was asked to report the reason(s) and situation(s) where samples were lost, reasons for reassay or why reassay could not be done, reassay curve, reassay values, reported values, and reasons for reported values.

The firm submitted tables which included sample identifications for all 32 samples listed as "lost in processing", reasons why study samples were coded lost in processing, reasons for reassay or why reassay could not be done, reassay values, reported values, and reasons for reported values.

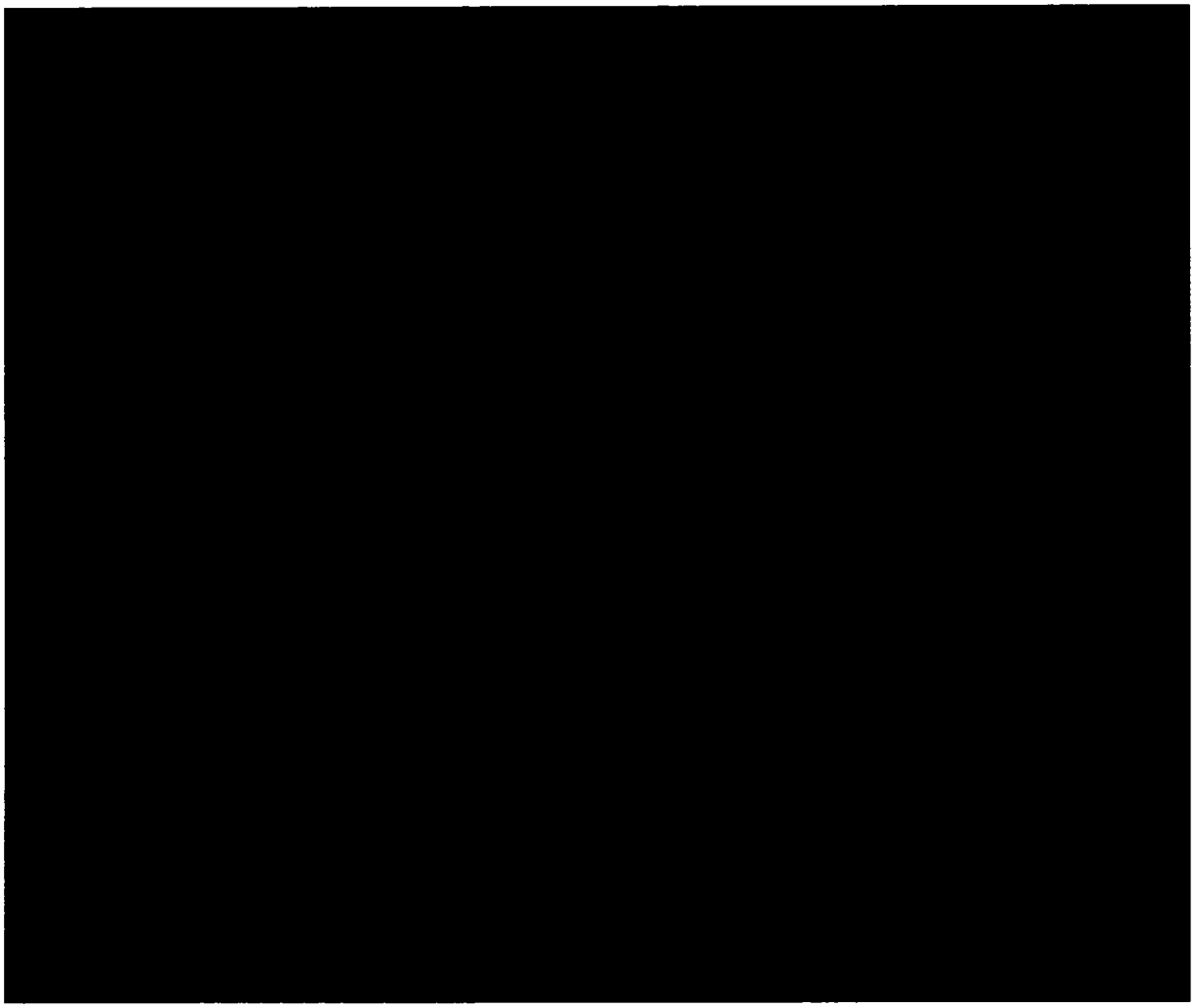
Reply to the Comment

The firm's response to the comment is acceptable.

Comment #3

The firm was asked to provide all data and calculations that justify the choice of the Wagner function as the regression

equation for analytical runs compared to other equation/weighting combinations.



Reply to the Comment

The firm's response to the comment is acceptable.

III. Recommendations:

1. The single-dose bioequivalence study #941316, conducted by Royce Laboratories, Inc., under fasting conditions, on its Guanfacine HCl 2 mg Tablets, lot #MD-1192, comparing it to Tenex® 2 mg Tablets manufactured by A.H. Robins has been found acceptable by the Division of Bioequivalence. The study demonstrates that Royce's Guanfacine HCl Tablets, 2 mg is bioequivalent to A.H. Robins's Tenex® 2 mg Tablets.

2. The dissolution testing conducting by Royce Laboratories, Inc., on its Guanfacine HCl, 2 mg and 1 mg Tablets, lot #MD-1192

and MD-1191, respectively, is acceptable. The formulation for the 1 mg strength is proportionally similar to the 2 mg strength of the test product which underwent acceptable bioequivalence testing. Waiver of the in vivo bioequivalence study requirements for the firm's Guanfacine HCl, 1 mg Tablets of the test product is granted. The Division of Bioequivalence deems Guanfacine HCl, Tablets 1 mg, manufactured by Royce Laboratories, Inc., to be bioequivalent to Tenex® Tablets 1 mg, manufactured by A.H. Robins.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 500 mL of water at 37°C using USP 23 apparatus II (paddle) at 50 rpm. The test product should meet the following specification:

> Not less than [redacted]Q) of the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

The firm should be informed of the above recommendations.

[redacted]
Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE [redacted] for KM Date: 11/1/96

Concur: [redacted] Date: 11/6/96
Rabindra Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

MMakary/10-8-96 wp 74762SDW.796
cc: ANDA #74-762, original, HFD-658 (Makary), Drug File, Division File.

MAR 1 1 1996

FILE COPY

Guanfacine Hydrochloride
1 & 2 mg tablets
ANDA #74-762
Reviewer: James D. Henderson
File: 74762SWD.095

Royce Laboratories
Miami, FL
Submitted:
October 3, 1995

SUMMARY

1. Bioequivalence Review No.: 1

2. Dates:

APPLICANT	FDA
Original Submission 10/3/95	Assigned to Reviewer 1/26/96
	Started by Reviewer 1/27/96
	RD Submitted 3/9/96
	RD Approved 3/11/96
	Final Submitted 3/11/96

3. Pharmacological Category, Rx or OTC: Rx, antihypertensive

4. Reference Listed Drug: Tenex® (AH Robins, NDA #19-032, 11/7/88); exclusivity for treatment of hypertension expires on 5/11/96

5. USP Monograph (Drug Product): none

6. Conclusion: Incomplete

DEFICIENCY COMMENTS:

1. The sponsor should repeat dissolution testing using 900 mL of medium and all other conditions the same.

2. The sponsor should describe the shipping conditions

3. [redacted]

4. [redacted]

5. Long-term frozen stability data should be reported.

6. For all 30 samples listed as "lost in processing", including nine predose samples, the sponsor should provide a table containing sample identifications, initial values, initial assay curve, reasons for reassay or why reassay could not be done, reassay curve, reassay values, reported values, and reasons for reported values.

7. All data and calculations that justify the choice of the Wagner function as the regression equation for analytical runs compared to other equation/weighting combinations should be provided.

7. Recommendations:

1. The bioequivalence study conducted by Royce Laboratories on its guanfacine hydrochloride 2 mg tablet, lot #MD-1192, comparing it to Tenex® 2 mg tablet, lot #0941035, has been found incomplete by the Division of Bioequivalence due to deficiencies 1-7.

2. The sponsor should be informed of deficiency comments 1-7 and recommendation 1.

8. Signature Blocks and Routing:

[redacted]

James D. Henderson, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED RPATNAIK
FT INITIALED RPATNAIK [redacted] 3/12/96

JDH/gj/3-11-96/74762

cc: ANDA #74-762 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-344 (CViswanathan), HFD-655 (Patnaik, Henderson), Drug File, Division File

STUDY SITES AND DATES

9. Clinical Site, Investigators, and Study Dates:

CLINICAL SITE: [redacted]

MEDICAL DIRECTO [redacted]
SCIENTIFIC DIRE [redacted]
PROTOCOL: #941316 (5/30/95); IRB approval 6/7/95
DOSING DATES: 6/15/95 and 6/29/95

10. Analytical Site, Investigators, and Analysis Dates:

ANALYTICAL SITE: [redacted]
ANALYTICAL DIRECTO [redacted]
ANALYSIS DATES: 7/10-9/5/95 (82 days frozen storage)

BIOSTUDY PRODUCT INFORMATION

11. Biostudy Products:

Product:	TEST (generic)	RLD (reference)
Drug Name	guanfacine HCl	Tenex®
Lot Number	#MD-1192 (Royce)	#0941035 (AHR)
Potency	100.7%	102.2%
Expiration Date	-	8/96
Manufacture Date		-
Batch Size (finished)	[redacted]	

12. Test Product Formulation: Table 1

13. Dissolution Testing: Table 2 (see Comments, #29.a.)

STUDY DESIGN AND PROCEDURES

14. Design:

CROSSOVER OR PARALLEL: randomized, two-way crossover (two treatments, periods, and sequences)

SINGLE OR MULTIPLE DOSE: single dose

FASTING OR FED: fasting

WASHOUT INTERVAL: 14 days

STUDY POPULATION: healthy adult male volunteers

TREATMENTS:

A. guanfacine hydrochloride tablets 2 mg (test), Royce lot #MD-1192, dose = 2 mg (1 tablet)

B. Tenex® 2 mg tablets (RLD), AH Robins lot #0941035 (exp 8/96), dose = 2 mg (1 tablet)

All doses were administered with 240 mL of water, and dosing occurred while subjects were seated in bed.

15. Subjects:

NUMBER OF SUBJECTS ENROLLED (PLANNED PLUS ALTERNATES), **COMPLETED, AND REASONS FOR DROPOUTS:**

The protocol states that 24 planned subjects plus two alternates (total of 26 subjects) were to be enrolled, and that samples from Subjects 1-24 would be assayed if they completed the study. Dropouts would be replaced prior to assay with alternates of the same sequence where possible.

Subject 14 (S14) was withdrawn from the study about 8 min before Period 1 dosing due to low BP (see #17.a. below). Therefore, only 25 subjects were dosed, with 24 subjects completing the crossover. S2 withdrew at 1.5 hr after Period 1 dosing due to medical events judged as not related to the study drug or procedures.

NUMBER OF DATA SETS ANALYZED AND REASONS:

Statistical and pharmacokinetic analysis was performed using data from 24 subjects (1, 3-13, 15-26). The study was unbalanced with 13 subjects in Sequence 1 (AB) and 11 subjects in Sequence 2 (BA).

INCLUSION CRITERIA:

- male volunteer, 18-45 years old
- weight at least 60 kg, and within ± 15% of ideal weight (Table of Desirable Weights of Adults, Metropolitan Life Insurance Company, 1983)
- good health as determined by medical history, physical examination, and laboratory tests (hematology, serum chemistry, urinalysis, HIV-AIDS test, 12-lead ECG)

EXCLUSION CRITERIA:

- history or presence of significant systemic, organ, or psychiatric disease
- history or presence of significant alcoholism or drug abuse within the last year
- hypersensitivity or idiosyncratic reaction to guanfacine HCl or other phenylacetyl-guanidine derivatives
- BP < 110/70 mm Hg at screening or < 100/60 mm Hg at predose vital sign determination
- pulse <= 50 bpm at screening or prior to dosing
- abnormal diet within the last four weeks prior to study start
- donation of > 500 mL blood in 14 days, 750 mL/3 months, 1000 mL/6 months, 1500 mL/9 months, 2000 mL/1 year, through completion of the study
- participation in another clinical trial within 28 days of study start

16. Study Procedures

RESTRICTIONS:

Subjects were confined to the clinical site from 12 hr predose until after the 36-hr draw, and then returned for the remaining samples. No medications of any kind were allowed for the 7 days preceding the study, not including vitamins taken as nutritional supplements in non-therapeutic doses. Consumption of alcoholic or xanthine-containing foods and beverages was prohibited for 24 hr before dosing and during the period of sample collection. Subjects remained seated in bed for the first 4 hr postdose, and then were allowed to engage in normal activity.

FOODS AND FLUIDS:

Subjects fasted from 10 hr predose until 4 hr postdose when a standardized meal schedule was begun. Water was prohibited from 2 hr predose until 4 hr postdose but was allowed freely at all other times.

MONITORING:

Sitting BP and heart rate was measured predose and at 1, 2, 3, 4, 6, 12, 24, and 36 hr postdose.

BLOOD SAMPLING:

Blood samples were collected into EDTA-vacutainers at 0 (predose), 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 16, 24, 36, 48, and 72 hr postdose. Samples were cooled in an ice bath

[redacted]

17. Clinical Conduct:

PROTOCOL DEVIATIONS:

a. Twenty-six subjects were enrolled as per protocol, but S14 was withdrawn immediately before Period 1 dosing due to low BP. Twenty-five subjects were dosed.

b. Three violations of the prohibitions on alcohol and xanthine consumption were noted. The reviewer concurs these examples are not likely to affect the study outcome.

c. All blood samples were collected within 2 min of their scheduled times, except 22 samples for Trt. A (3-41 minutes late, 2 sample times not recorded) and 10 samples for Trt. B (3-15 minutes late, one sample time not recorded). In these cases, actual sample times were used for calculations; when times were not recorded, the scheduled time was used.

ADVERSE REACTIONS:

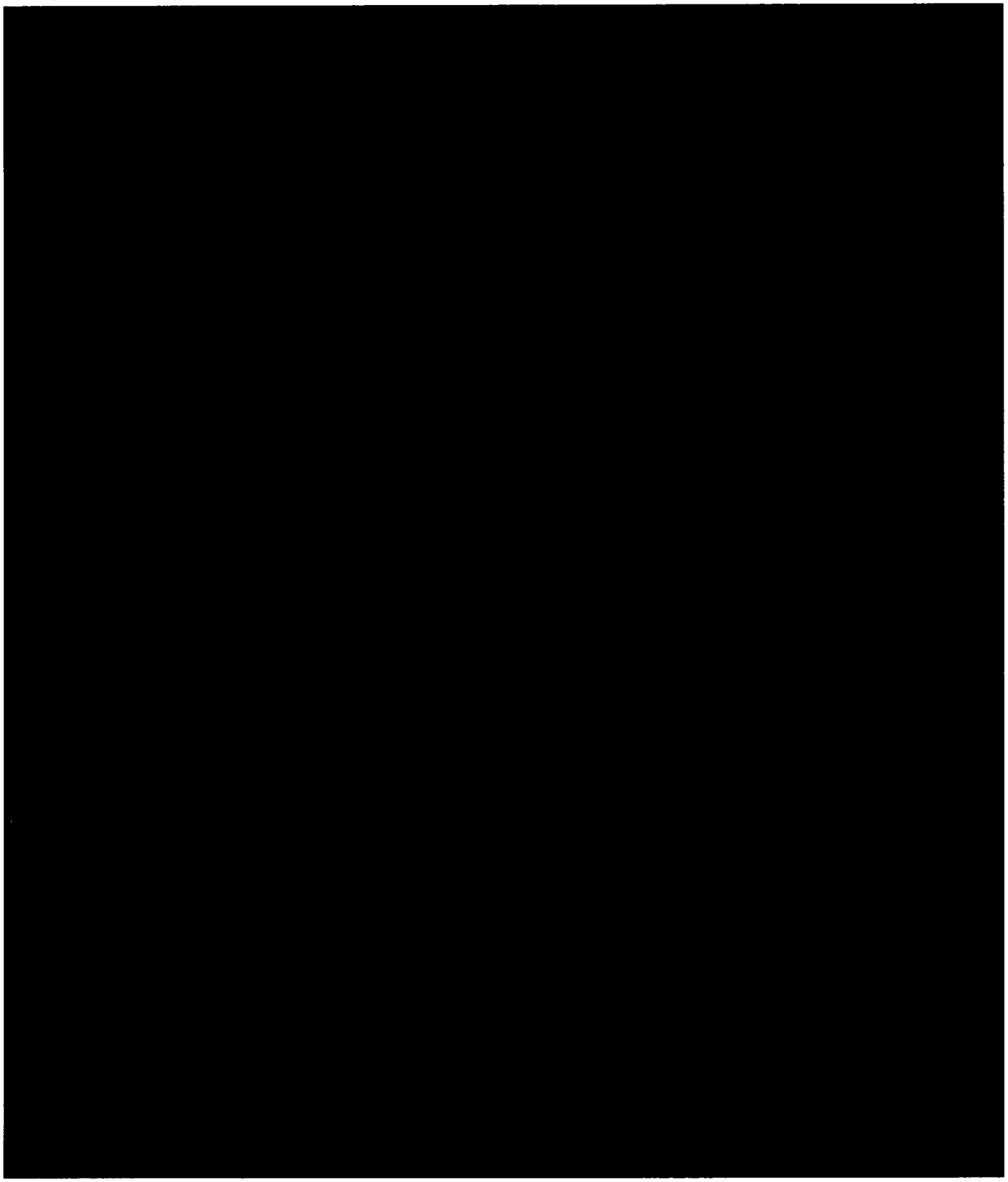
Trt. A: Six events, all rated as not serious, were reported involving five subjects. Five events were rated as mild intensity and one event as moderate intensity. One event was judged as caused by the drug (headache), two events due to the procedure (dizzy during blood draw), and three events were judged as due to other causality (headache (2), bloody stool). No drug treatment was required in any case.

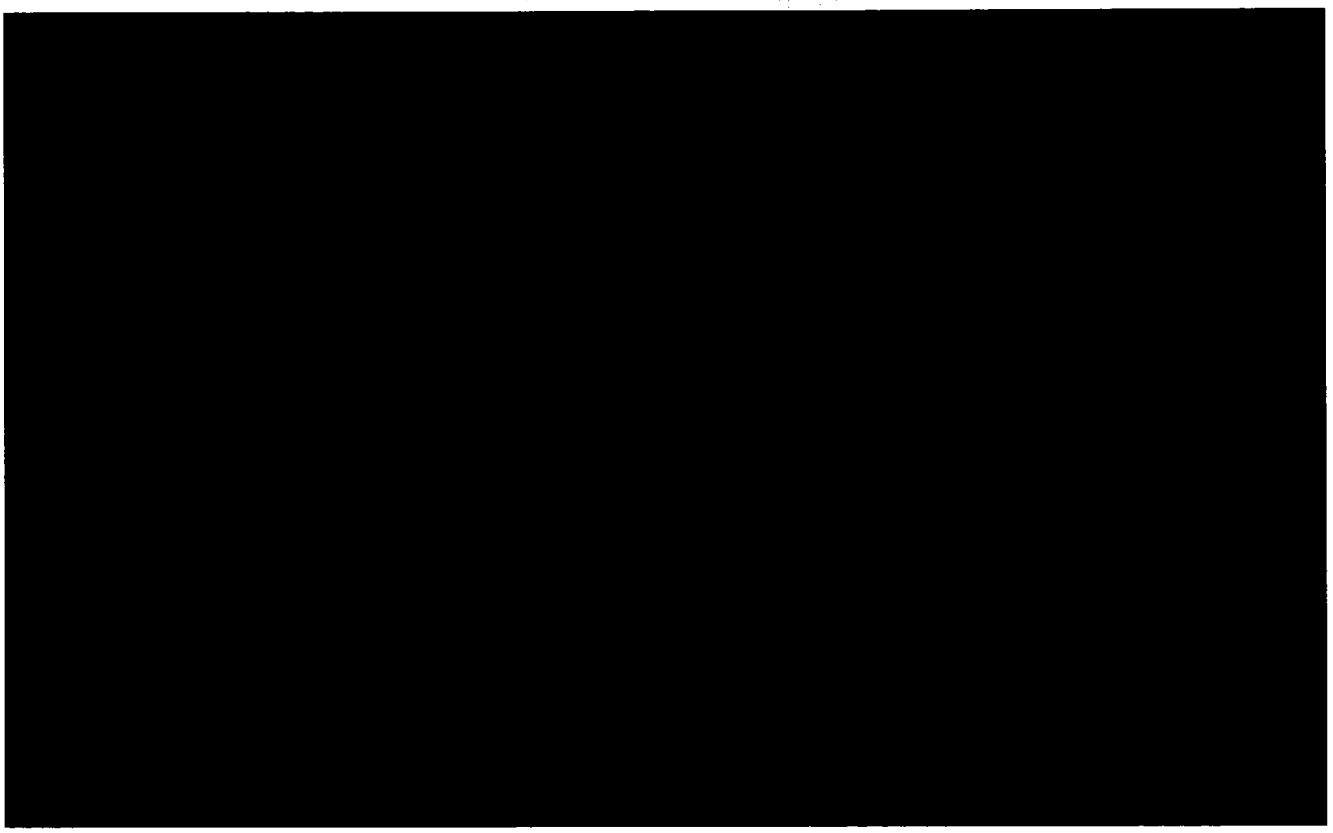
Trt. B: Eight events, all rated as not serious, were reported involving six subjects. All events were rated as mild intensity. Two events were judged as caused by the drug (lightheaded), and six events were judged as due to other causality (nausea (2), blurred vision, headache (2), other). No drug treatment was required in any case.

ANALYTICAL METHODOLOGY AND RESULTS

18. Summary of Method:

[redacted]





DATA ANALYSIS

25. Pharmacokinetic Parameters Analyzed:

- AUC0-t, linear trapezoidal method to the time t of the last measurable concentration (CLAST)
- AUCINF = AUC0-t + CLAST/KEL
- CMAX, TMAX from the observed data
- KEL, terminal elimination rate constant calculated from linear regression (logC vs. t) of the last 3 or more points
- HALF = log(2)/KEL

26. Summary of Statistical Analysis:

DESCRIPTION OF STATISTICAL MODEL:

- ANOVA performed for untransformed and log-transformed AUC's and CMAX using SAS GLM procedure with main effects of sequence, subjects within sequence, period, and treatment
- significance of sequence effect (10% level) tested against subjects within sequence as the error term; all other effects tested at 5% level against the mean square error term

CALCULATIONS:

- least-squares means (LSM), adjusted estimates of treatment differences and their standard errors
- 90% confidence intervals (CI) for estimated treatment differences

27. Pharmacokinetics/Statistics Results:

MEAN DRUG CONCENTRATIONS: Table 3

There were no instances of the first nonzero concentration as CMAX. The sponsor reported four instances of nonzero predose concentrations: Period 1, Subjects 4, 7, and 26; Period 2, S7. (See Comment 32.b. for discussion)

MEAN PHARMACOKINETIC PARAMETERS: Table 4

Statistically significant effects were noted for:

- sequence ($p < 0.1$): AUC0-t, AUCINF, and their log-transformed parameters
- period ($p < 0.05$): AUC0-t, AUCINF, and their log-transformed parameters
- treatment ($p < 0.05$): **AUC0-t, AUCINF, CMAX, logAUC0-t, logCMAX**

TEST/REFERENCE RATIOS: Table 5

WAIVER REQUEST

28. The sponsor has requested waiver of in vivo bioequivalence study requirements for its test product guanfacine hydrochloride 1 mg tablets, under 21 CFR 320.22(d)(2) as follows:

- bioequivalence of the test product guanfacine HCl 2 mg tablets to the RLD has been demonstrated
- both the 1 and 2 mg tablets of the test product meet an appropriate in vitro dissolution test
- both strengths of the test product are proportionately similar in their active and inactive ingredients

COMMENTS

29. Product Information:

a. Dissolution testing was conducted using the firm's in-house

method which differs from that used by FDA in that the firm used 500 mL medium (p. 123) and FDA recommends 900 mL.

NOTE: THIS PARAGRAPH FOR INTERNAL USE ONLY

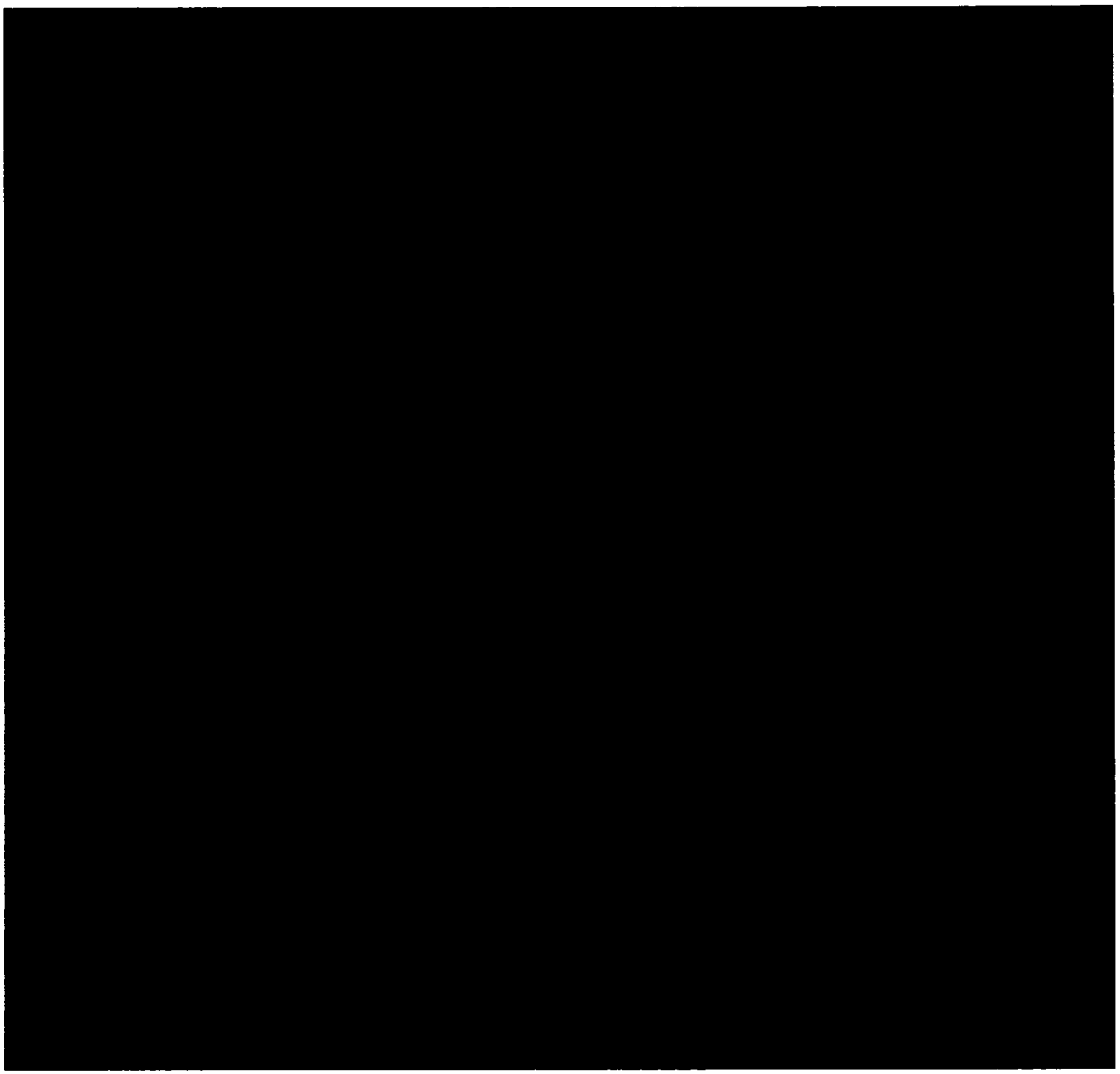
[redacted]

b. Waiver: Comparison of the formulations in Table 1 shows that the excipient compositions of the 1 and 2 mg strengths are identical except the colorants and a minor difference in the amount of filler.

30. Clinical Conduct: None

31. Analytical Results:

[redacted]



32. Pharmacokinetics/Statistics:

a. The reviewer repeated the SAS analysis using the GLM procedure with the data provided by the sponsor on diskette, and obtained essentially the same values for 90% CI's as reported. The 90% CI's after exclusion of S7 (see 24., samples not reportable) were: logAUC0-t, 100.8-108.0; logAUCINF, 100.5-107.8; logCMAX, 100.3-111.5.

b. On p. 364, Statistical Report, the sponsor notes four instances of nonzero predose samples (4-0-1, 7-0-1, 26-0-1, 7-0-

2) which were designated in the final report as not reportable. On p. 720, Analytical Report, samples 4-0-1 and 26-0-1 are described as lost in processing and not repeated due to insufficient volume. Samples 7-0-1 and 7-0-2 are described as requiring a dilution due to insufficient volume with determined values that were BLQ. Apparently, it is unknown if any of these predose samples actually had nonzero concentrations.

For these four samples, no initial assay values are reported in the Raw Data tables. It is noted that statistically significant sequence effects occurred for AUC0-t, AUCINF, and their log-transformed values.

33. Consults: none

prepared by [redacted] 3-11-96

James D. Henderson, Ph.D.
Review Branch II
Division of Bioequivalence

Table 1 - Test Product Formulation

FOR INTERNAL USE ONLY

INGREDIENT	TEST PRODUCT (2 mg STRENGTH) (mg/unit)	TEST PRODUCT (1 mg STRENGTH) (mg/unit)
CORE:		
guanfacine hydrochloride	2.3 (equivalent to 2 mg guanfacine base)	1.15 (equivalent to 1 mg guanfacine base)
microcrystalline cellulose, NF [redacted]	[redacted]	
FD&C Red #40 [redacted]		
D&C Yellow #10 Al- [redacted]		
lactose monohydrate, NF [redacted]		
povidone, USP		
crospovidone, NF		
stearic acid, NF		
magnesium stearate, NF		
total weight (mg)	120.0	120.0

Table 2. In Vitro Dissolution Testing

Drug (Generic Name): guanfacine hydrochloride
Strength/Dosage Form: 1 & 2 mg tablets
ANDA No.: 74-762
Firm: Royce
Submission Date: 10/3/95
File Name: 74762SDW.095

I. Dissolution Testing (Firm's Method):

USP 23 Basket: Paddle: X RPM: 50
No. Units Tested: 12
Volume and Medium: 500 mL water
Specifications: NLT [redacted] 45 min
Reference Drug: Tenex® (AH Robins)
Assay Methodology: [redacted]

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot #MD-1192 Strength (mg) 2			Reference Product exp 8/96 Lot #0941035 Strength (mg) 2		
	Mean %	Range	%CV	Mean %	Range	%CV
15	92.5	[redacted]	6.4	69.6	[redacted]	15.1
30	98.2		3.1	90.9		8.2
45	99.8		2.8	97.4		4.2
60	100.3		2.7	99.6		2.6

Sampling Times (Minutes)	Test Product Lot #MD-1191 Strength (mg) 1			Reference Product exp 7/96 Lot #940844 Strength (mg) 1		
	Mean %	Range	%CV	Mean %	Range	%CV
15	86.0	[redacted]	6.6	75.5	[redacted]	6.1
30	92.7		3.0	90.6		2.8
45	94.4		3.3	93.9		1.7
60	95.6		3.9	95.5		1.6

Table 3 - Mean Reported Plasma Guanfacine Concentrations (ng/mL, Fasting Study, N = 24)

Time (hr)	Trt. A (mean)	(test) CV(%)	Trt. B (mean)	(ref.) CV(%)	% Diff.
0	0.0	-	0.0	-	-
0.5	1.105	82[1]	0.775	84[2]	42.58
1	2.893	36	2.699	44	7.188
1.5	3.715	23	3.453	28	7.588
2	4.048	24	3.895	25	3.928
2.5	4.483	28	4.069	22	10.17
3	4.087	21	4.101	22	-0.34
3.5	4.292	22	4.056	19	5.819
4	4.243	24	4.045	21	4.895
5	3.832	22	3.84	17[2]	-0.21
6	3.547	21	3.358	16	5.628
8	3.142	19	3.091	19	1.65
12	2.495	23	2.326	19	7.266
16	1.875	26	1.709	23	9.713
24	1.16	24[2]	1.12	26[2]	3.571
36	0.601	34[2]	0.567	25[1]	5.996
48	0.326	45[2]	0.313	36[2]	4.153
72	0.095	88[2]	0.09	92[2]	5.556

[1] N = 22 [2] N = 23

Trt. A =
Trt. B =

Table 4 - Mean Reported Pharmacokinetic Parameters for Guanfacine (N = 24, Fasting Study)

Parameter[1]	Trt. A (mean)[2]	test CV(%)	Trt. B (mean)	ref. CV(%)	[3]	90% CI
AUC0-T	78.87	22	74.82	23	5.413	101.8-108.3
logAUC0-T	-	-	-	-	1.049	101.4-108.6
AUCINF	83.89	20[4]	79.55	20	5.456	101.1-107.7
logAUCINF	-	-	-	-	1.041	100.5-107.8
CMAX	4.847	26	4.482	21	8.144	101.3-114.0
logCMAX	-	-	-	-	1.066	101.2-112.2
TMAX (hr)	2.854	36	2.958	35	-3.52	-
KEL (hr^{-1})	0.05369	22[4]	0.05222	20	2.815	-
HALF (hr)	13.473	21[4]	13.777	20	-2.26	-

[1] units: AUC, ng*hr/mL; CMAX, ng/mL

[2] Arithmetic means are reported.

[3] For untransformed data, the % difference is calculated as $(A_{mean} - B_{mean})*100/B_{mean}$. For log-transformed values, the ratio of least squares geometric means is reported as exp(ESTIMATE) where the ESTIMATE is obtained from the ANOVA.

[4] N = 23

Trt. A = guanfacine HCl 2 mg tablet, Royce
Trt. B = Tenex® 2 mg tablet, AH Robins

Table 5 - T/R Ratios

Subject	AUC0-T	AUCINF	CMAX
1	[redacted]		
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
15			
16			
17			
18			
19			
20			
21			
22			
23			
24			
25			
26			
< 75%	0	0	0
75-125%	24	24	19
> 125%	0	0	5

Table 6 - Results of Prestudy Validation

FOR INTERNAL USE ONLY

MAR 1 1 1996

Guanfacine Hydrochloride
1 & 2 mg tablets
ANDA #74-762
Reviewer: James D. Henderson
File: 74762SWD.095

Royce Laboratories
Miami, FL
Submitted:
October 3, 1995

SUMMARY

1. Bioequivalence Review No.: 1

2. Dates:

APPLICANT	FDA
Original Submission 10/3/95	Assigned to Reviewer 1/26/96
	Started by Reviewer 1/27/96
	RD Submitted 3/9/96
	RD Approved 3/11/96
	Final Submitted 3/11/96

3. Pharmacological Category, Rx or OTC: Rx, antihypertensive

4. Reference Listed Drug: Tenex® (AH Robins, NDA #19-032, 11/7/88); exclusivity for treatment of hypertension expires on 5/11/96

5. USP Monograph (Drug Product): none

6. Conclusion: Incomplete

DEFICIENCY COMMENTS:

1. The sponsor should repeat dissolution testing using 900 mL of medium and all other conditions the same.

2. The sponsor should describe the shipping conditions used to transport samples from the [redacted] to the Quebec analytical site.

3. [redacted]

[redacted]

4. [redacted]

5. [redacted]

6. For all 30 samples listed as "lost in processing", including nine predose samples, the sponsor should provide a table containing sample identifications, initial values, initial assay curve, reasons for reassay or why reassay could not be done, reassay curve, reassay values, reported values, and reasons for reported values.

7. All data and calculations that justify the choice of the Wagner function as the regression equation for analytical runs compared to other equation/weighting combinations should be provided.

7. Recommendations:

1. The bioequivalence study conducted by Royce Laboratories on its guanfacine hydrochloride 2 mg tablet, lot #MD-1192, comparing it to Tenex® 2 mg tablet, lot #0941035, has been found incomplete by the Division of Bioequivalence due to deficiencies 1-7.

2. The sponsor should be informed of deficiency comments 1-7 and recommendation 1.

8. Signature Blocks and Routing:

[redacted]

James D. Henderson, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED RPATNAIK
FT INITIALED RPATNAIK [redacted] 3/12/96

JDH/gj/3-11-96/74762

cc: ANDA #74-762 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-344 (CViswanathan), HFD-655 (Patnaik, Henderson), Drug File, Division File

STUDY SITES AND DATES

9. Clinical Site, Investigators, and Study Dates:

CLINICAL SITE: [redacted]

MEDICAL DIRECTO [redacted]
SCIENTIFIC DIRECTOR: [redacted]
PROTOCOL: #941316 (5/30/95); IRB approval 6/7/95
DOSING DATES: 6/15/95 and 6/29/95

10. Analytical Site, Investigators, and Analysis Dates:

ANALYTICAL SITE: [redacted]
ANALYTICAL DIRECT [redacted]
ANALYSIS DATES: 7/10-9/5/95 (82 days frozen storage)

BIOSTUDY PRODUCT INFORMATION

11. Biostudy Products:

Product:	TEST (generic)	RLD (reference)
Drug Name	guanfacine HCl	Tenex®
Lot Number	#MD-1192 (Royce)	#0941035 (AHR)
Potency	100.7%	102.2%
Expiration Date	-	8/96
Manufacture Date		-
Batch Size (finished)	[redacted]	

12. Test Product Formulation: Table 1

13. Dissolution Testing: Table 2 (see Comments, #29.a.)

STUDY DESIGN AND PROCEDURES

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SINGLE OR MULTIPLE DOSE: single dose

FASTING OR FED: fasting

WASHOUT INTERVAL: 14 days

STUDY POPULATION: healthy adult male volunteers

TREATMENTS:

A. guanfacine hydrochloride tablets 2 mg (test), Royce lot #MD-1192, dose = 2 mg (1 tablet)

B. Tenex® 2 mg tablets (RLD), AH Robins lot #0941035 (exp 8/96), dose = 2 mg (1 tablet)

All doses were administered with 240 mL of water, and dosing occurred while subjects were seated in bed.

15. Subjects:

NUMBER OF SUBJECTS ENROLLED (PLANNED PLUS ALTERNATES), **COMPLETED, AND REASONS FOR DROPOUTS:**

The protocol states that 24 planned subjects plus two alternates (total of 26 subjects) were to be enrolled, and that samples from Subjects 1-24 would be assayed if they completed the study. Dropouts would be replaced prior to assay with alternates of the same sequence where possible.

Subject 14 (S14) was withdrawn from the study about 8 min before Period 1 dosing due to low BP (see #17.a. below). Therefore, only 25 subjects were dosed, with 24 subjects completing the crossover. S2 withdrew at 1.5 hr after Period 1 dosing due to medical events judged as not related to the study drug or procedures.

NUMBER OF DATA SETS ANALYZED AND REASONS:

Statistical and pharmacokinetic analysis was performed using data from 24 subjects (1, 3-13, 15-26). The study was unbalanced with 13 subjects in Sequence 1 (AB) and 11 subjects in Sequence 2 (BA).

INCLUSION CRITERIA:

- male volunteer, 18-45 years old
- weight at least 60 kg, and within ± 15% of ideal weight (Table of Desirable Weights of Adults, Metropolitan Life Insurance Company, 1983)
- good health as determined by medical history, physical examination, and laboratory tests (hematology, serum chemistry, urinalysis, HIV-AIDS test, 12-lead ECG)

EXCLUSION CRITERIA:

- history or presence of significant systemic, organ, or psychiatric disease
- history or presence of significant alcoholism or drug abuse within the last year
- hypersensitivity or idiosyncratic reaction to guanfacine HCl or other phenylacetyl-guanidine derivatives
- BP < 110/70 mm Hg at screening or < 100/60 mm Hg at predose vital sign determination
- pulse <= 50 bpm at screening or prior to dosing
- abnormal diet within the last four weeks prior to study start
- donation of > 500 mL blood in 14 days, 750 mL/3 months, 1000 mL/6 months, 1500 mL/9 months, 2000 mL/1 year, through completion of the study
- participation in another clinical trial within 28 days of study start

16. Study Procedures

RESTRICTIONS:

Subjects were confined to the clinical site from 12 hr predose until after the 36-hr draw, and then returned for the remaining samples. No medications of any kind were allowed for the 7 days preceding the study, not including vitamins taken as nutritional supplements in non-therapeutic doses. Consumption of alcoholic or xanthine-containing foods and beverages was prohibited for 24 hr before dosing and during the period of sample collection. Subjects remained seated in bed for the first 4 hr postdose, and then were allowed to engage in normal activity.

FOODS AND FLUIDS:

Subjects fasted from 10 hr predose until 4 hr postdose when a standardized meal schedule was begun. Water was prohibited from 2 hr predose until 4 hr postdose but was allowed freely at all other times.

MONITORING:

Sitting BP and heart rate was measured predose and at 1, 2, 3, 4, 6, 12, 24, and 36 hr postdose.

BLOOD SAMPLING:

Blood samples were collected into EDTA-vacutainers at 0 (predose), 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 16, 24, 36, 48, and 72 hr postdose. Samples were cooled in an ice bath

[redacted]

17. Clinical Conduct:

PROTOCOL DEVIATIONS:

a. Twenty-six subjects were enrolled as per protocol, but S14 was withdrawn immediately before Period 1 dosing due to low BP. Twenty-five subjects were dosed.

b. Three violations of the prohibitions on alcohol and xanthine consumption were noted. The reviewer concurs these examples are not likely to affect the study outcome.

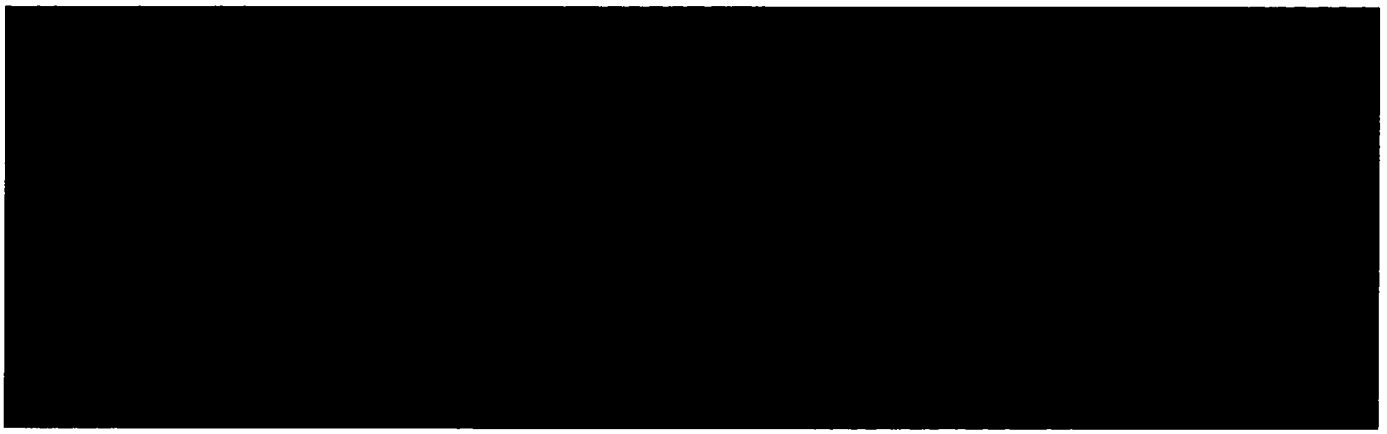
c. All blood samples were collected within 2 min of their scheduled times, except 22 samples for Trt. A (3-41 minutes late, 2 sample times not recorded) and 10 samples for Trt. B (3-15 minutes late, one sample time not recorded). In these cases, actual sample times were used for calculations; when times were not recorded, the scheduled time was used.

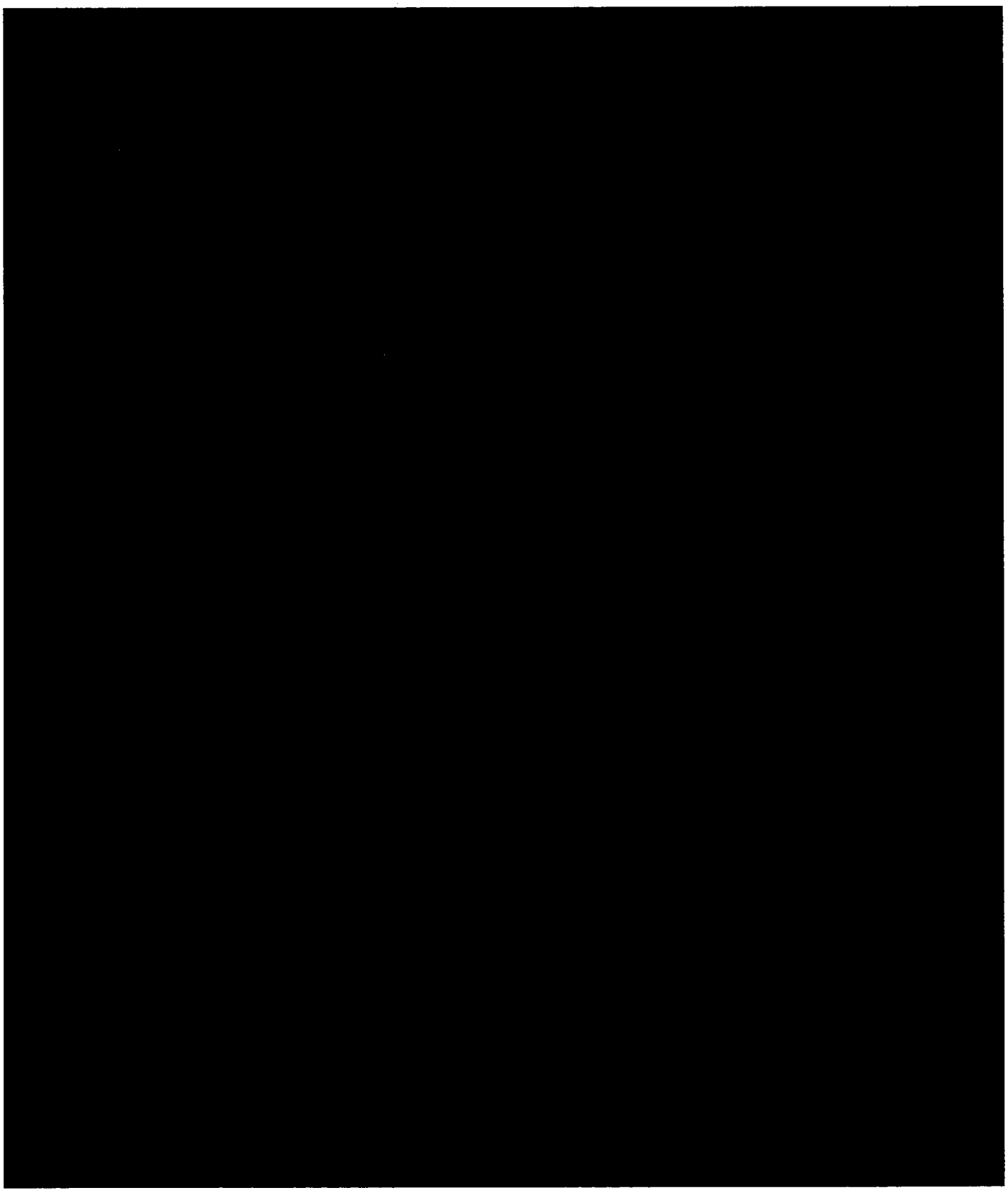
ADVERSE REACTIONS:

Trt. A: Six events, all rated as not serious, were reported involving five subjects. Five events were rated as mild intensity and one event as moderate intensity. One event was judged as caused by the drug (headache), two events due to the procedure (dizzy during blood draw), and three events were judged as due to other causality (headache (2), bloody stool). No drug treatment was required in any case.

Trt. B: Eight events, all rated as not serious, were reported involving six subjects. All events were rated as mild intensity. Two events were judged as caused by the drug (lightheaded), and six events were judged as due to other causality (nausea (2), blurred vision, headache (2), other). No drug treatment was required in any case.

ANALYTICAL METHODOLOGY AND RESULTS





DATA ANALYSIS

25. Pharmacokinetic Parameters Analyzed:

- AUC0-t, linear trapezoidal method to the time t of the last measurable concentration (CLAST)
- AUCINF = AUC0-t + CLAST/KEL
- CMAX, TMAX from the observed data
- KEL, terminal elimination rate constant calculated from linear regression (logC vs. t) of the last 3 or more points
- HALF = log(2)/KEL

26. Summary of Statistical Analysis:

DESCRIPTION OF STATISTICAL MODEL:

- ANOVA performed for untransformed and log-transformed AUC's and CMAX using SAS GLM procedure with main effects of sequence, subjects within sequence, period, and treatment
- significance of sequence effect (10% level) tested against subjects within sequence as the error term; all other effects tested at 5% level against the mean square error term

CALCULATIONS:

- least-squares means (LSM), adjusted estimates of treatment differences and their standard errors
- 90% confidence intervals (CI) for estimated treatment differences

27. Pharmacokinetics/Statistics Results:

MEAN DRUG CONCENTRATIONS: Table 3

There were no instances of the first nonzero concentration as CMAX. The sponsor reported four instances of nonzero predose concentrations: Period 1, Subjects 4, 7, and 26; Period 2, S7. (See Comment 32.b. for discussion)

MEAN PHARMACOKINETIC PARAMETERS: Table 4

Statistically significant effects were noted for:

- sequence ($p < 0.1$): AUC0-t, AUCINF, and their log-transformed parameters
- period ($p < 0.05$): AUC0-t, AUCINF, and their log-transformed parameters
- treatment ($p < 0.05$): AUC0-t, AUCINF, CMAX, logAUC0-t, logCMAX

TEST/REFERENCE RATIOS: Table 5

WAIVER REQUEST

28. The sponsor has requested waiver of in vivo bioequivalence study requirements for its test product guanfacine hydrochloride 1 mg tablets, under 21 CFR 320.22(d)(2) as follows:

- bioequivalence of the test product guanfacine HCl 2 mg tablets to the RLD has been demonstrated
- both the 1 and 2 mg tablets of the test product meet an appropriate in vitro dissolution test
- both strengths of the test product are proportionately similar in their active and inactive ingredients

COMMENTS

29. Product Information:

a. Dissolution testing was conducted using the firm's in-house

method which differs from that used by FDA in that the firm used 500 mL medium (p. 123) and FDA recommends 900 mL.

NOTE: THIS PARAGRAPH FOR INTERNAL USE ONLY

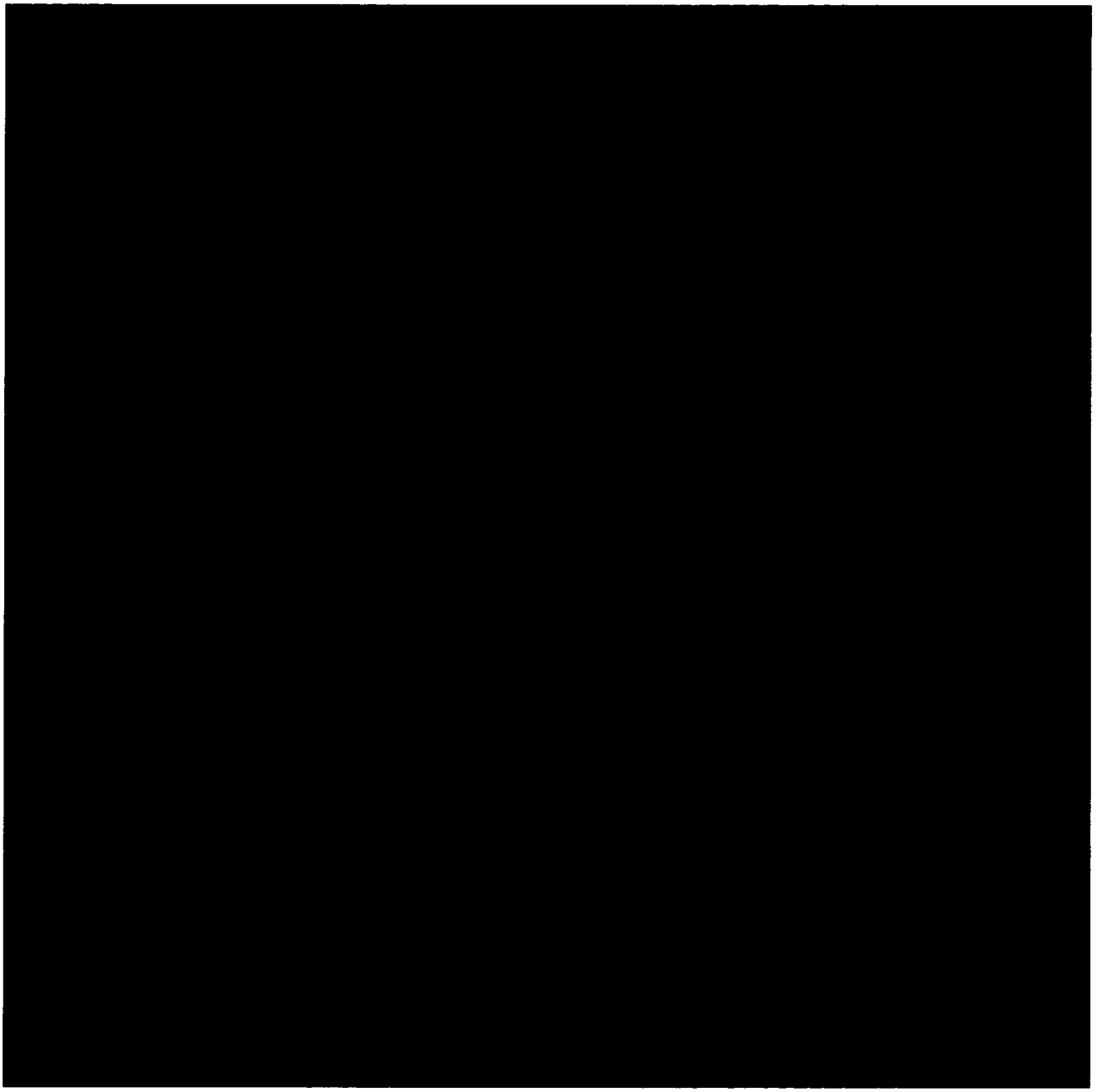
[redacted]

b. Waiver: Comparison of the formulations in Table 1 shows that the excipient compositions of the 1 and 2 mg strengths are identical except the colorants and a minor difference in the amount of filler.

30. Clinical Conduct: None

31. Analytical Results:

[redacted]



32. Pharmacokinetics/Statistics:

a. The reviewer repeated the SAS analysis using the GLM procedure with the data provided by the sponsor on diskette, and obtained essentially the same values for 90% CI's as reported. The 90% CI's after exclusion of S7 (see 24., samples not reportable) were: logAUC0-t, 100.8-108.0; logAUCINF, 100.5-107.8; logCMAX, 100.3-111.5.

b. On p. 364, Statistical Report, the sponsor notes four instances of nonzero predose samples (4-0-1, 7-0-1, 26-0-1, 7-0-

2) which were designated in the final report as not reportable. On p. 720, Analytical Report, samples 4-0-1 and 26-0-1 are described as lost in processing and not repeated due to insufficient volume. Samples 7-0-1 and 7-0-2 are described as requiring a dilution due to insufficient volume with determined values that were BLQ. Apparently, it is unknown if any of these predose samples actually had nonzero concentrations.

For these four samples, no initial assay values are reported in the Raw Data tables. It is noted that statistically significant sequence effects occurred for AUC0-t, AUCINF, and their log-transformed values.

33. Consults: none

prepared by [redacted] 3-11-96

James D. Henderson, Ph.D.
Review Branch II
Division of Bioequivalence

Table 1 - Test Product Formulation

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INGREDIENT	TEST PRODUCT (2 mg STRENGTH) (mg/unit)	TEST PRODUCT (1 mg STRENGTH) (mg/unit)
CORE:		
guanfacine hydrochloride	2.3 (equivalent to 2 mg guanfacine base)	1.15 (equivalent to 1 mg guanfacine base)
microcrystalline cellulose, NF [redacted]	[redacted]	
FD&C Red #40 [redacted]		
D&C Yellow #1[redacted] lake		
lactose monohydrate, [redacted]		
povidone, USP		
crospovidone, NF		
stearic acid, NF		
magnesium stearate, NF		
total weight (mg)	120.0	120.0

Table 2. In Vitro Dissolution Testing

Drug (Generic Name): guanfacine hydrochloride
Strength/Dosage Form: 1 & 2 mg tablets
ANDA No.: 74-762
Firm: Royce
Submission Date: 10/3/95
File Name: 74762SDW.095

I. Dissolution Testing (Firm's Method):

USP 23 Basket: Paddle: X RPM: 50
No. Units Tested: 12
Volume and Medium: 500 mL water
Specifications: NLT [redacted] 5 min
Reference Drug: Tenex® (AH Robins)
Assay Methodology: [redacted]

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot #MD-1192 Strength (mg) 2			Reference Product exp 8/96 Lot #0941035 Strength (mg) 2		
	Mean %	Range	%CV	Mean %	Range	%CV
15	92.5	[redacted]	6.4	69.6	[redacted]	15.1
30	98.2		3.1	90.9		8.2
45	99.8		2.8	97.4		4.2
60	100.3		2.7	99.6		2.6

Sampling Times (Minutes)	Test Product Lot #MD-1191 Strength (mg) 1			Reference Product exp 7/96 Lot #940844 Strength (mg) 1		
	Mean %	Range	%CV	Mean %	Range	%CV
15	86.0	[redacted]	6.6	75.5	[redacted]	6.1
30	92.7		3.0	90.6		2.8
45	94.4		3.3	93.9		1.7
60	95.6		3.9	95.5		1.6

Table 3 - Mean Reported Plasma Guanfacine Concentrations (ng/mL, Fasting Study, N = 24)

Time (hr)	Trt. A (mean)	(test) CV(%)	Trt. B (mean)	(ref.) CV(%)	% Diff.
0	0.0	-	0.0	-	-
0.5	1.105	82[1]	0.775	84[2]	42.58
1	2.893	36	2.699	44	7.188
1.5	3.715	23	3.453	28	7.588
2	4.048	24	3.895	25	3.928
2.5	4.483	28	4.069	22	10.17
3	4.087	21	4.101	22	-0.34
3.5	4.292	22	4.056	19	5.819
4	4.243	24	4.045	21	4.895
5	3.832	22	3.84	17[2]	-0.21
6	3.547	21	3.358	16	5.628
8	3.142	19	3.091	19	1.65
12	2.495	23	2.326	19	7.266
16	1.875	26	1.709	23	9.713
24	1.16	24[2]	1.12	26[2]	3.571
36	0.601	34[2]	0.567	25[1]	5.996
48	0.326	45[2]	0.313	36[2]	4.153
72	0.095	88[2]	0.09	92[2]	5.556

[1] N = 22 [2] N = 23

Trt. A =
Trt. B =

Table 4 - Mean Reported Pharmacokinetic Parameters for Guanfacine (N = 24, Fasting Study)

Parameter[1]	Trt. A (mean)[2]	test CV(%)	Trt. B (mean)	ref. CV(%)	[3]	90% CI
AUC0-T	78.87	22	74.82	23	5.413	101.8-108.3
logAUC0-T	-	-	-	-	1.049	101.4-108.6
AUCINF	83.89	20[4]	79.55	20	5.456	101.1-107.7
logAUCINF	-	-	-	-	1.041	100.5-107.8
CMAX	4.847	26	4.482	21	8.144	101.3-114.0
logCMAX	-	-	-	-	1.066	101.2-112.2
TMAX (hr)	2.854	36	2.958	35	-3.52	-
KEL (hr^{-1})	0.05369	22[4]	0.05222	20	2.815	-
HALF (hr)	13.473	21[4]	13.777	20	-2.26	-

[1] units: AUC, ng*hr/mL; CMAX, ng/mL

[2] Arithmetic means are reported.

[3] For untransformed data, the % difference is calculated as $(A_{mean} - B_{mean})*100/B_{mean}$. For log-transformed values, the ratio of least squares geometric means is reported as exp(ESTIMATE) where the ESTIMATE is obtained from the ANOVA.

[4] N = 23

Trt. A = guanfacine HCl 2 mg tablet, Royce
Trt. B = Tenex® 2 mg tablet, AH Robins

Table 5 - T/R Ratios

Subject	AUC0-T	AUCINF	CMAX
1	[redacted]		
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
15			
16			
17			
18			
19			
20			
21			
22			
23			
24			
25			
26			
< 75%	0	0	0
75-125%	24	24	19
> 125%	0	0	5

Table 6 - Results of Prestudy Validation

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